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Therapeutic Class Review
Multiple Sclerosis Biologic Response Modifiers

Overview/Summary

The biologic response modifiers are Food and Drug Administration (FDA) approved for the treatment of relapsing remitting Multiple Sclerosis (MS) and include glatiramer acetate (Copaxone®) and interferons beta-1b (Betaseron®) and beta-1a (Rebif® and Avonex®).[1-4] Moreover, interferon beta-1b (Betaseron®) and interferon beta-1a (Avonex®) are FDA approved for the treatment of patients with first clinical episode and magnetic resonance imaging (MRI) evidence of MS, often referred to as a clinically isolated syndrome (CIS).[1,3,5] The exact mechanisms of action of the interferons and glatiramer acetate are unknown but are likely due to antiproliferative and immunomodulatory effects.[6-7] Glatiramer acetate is a polymer containing four amino acids that are found in the myelin basic protein.[4,6] Interferons are produced by recombinant deoxyribonucleic acid (DNA) technology in different cell systems, resulting in slight differences in amino acid sequence, molecular weight, degree of glycosylation and specific activity.[1-3] Specific activity is based on proportional relation to the potency of the antiviral activity of the World Health Organization (WHO) reference standard of human interferon and expressed as millions of international units (MIU).[1-3] Each interferon beta product is FDA approved for use at different doses and with different administration schedules. Interferon beta-1a (Avonex®) 30 µg (6 MIU) is administered intramuscularly once weekly, while interferon beta-1a (Rebif®) 22-44 µg (6-12 MIU) is administered three times weekly and interferon beta-1b (Betaseron®) 250 µg (8 MIU) is administered every other day subcutaneously.[1-3] The most common adverse effects of interferon therapy are influenza-type symptoms, injection site reactions, headache, nausea and muskoloskeletal pain. Rare cases of hepatic toxicity have occurred in patients who were treated with interferon therapy. Moreover, interferon therapy should be used with caution in patients with depression or other mood disorders. Patients receiving glatiramer acetate therapy may experience a transient, self-limiting post-injection, systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction and urticaria.[4] There are no known drug interactions with glatiramer acetate therapy. In addition, glatiramer acetate therapy is not associated with an increased risk of hepatotoxicity or depression.

MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.[8-10] Symptoms of MS can include limb sensory disturbances, optic nerve dysfunction, pyramidal tract dysfunction, bladder/bowel dysfunction, sexual dysfunction, ataxia, and diplopia.[10] There are four clinical subtypes of MS: relapsing-remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS) and secondary progressive (SPMS).[8-10] RRMS is the most common form and is characterized by acute relapses followed by partial or full recovery.[10-11] RRMS patients remain relatively stable between attacks. PPMS is characterized by a continuous, gradual decline in function without evidence of acute attacks. PRMS patients also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.[10]

An approach to treating patients with MS includes management of symptoms, treatment of acute relapses and utilization of disease-modifying therapies to reduce the frequency and severity of relapses and delay disease and disability progression.[6,8,10] The American Academy of Neurology and the MS Society guidelines recommend the use of interferons or glatiramer acetate as first-line therapy in all patients with clinically definite RRMS and in select patients with CIS.[10] No preference is given to any one mode of therapy. It is suggested that the most appropriate agent may be selected on an individual basis and

monitored for clinical response and tolerability. Numerous head-to-head studies have found therapy with interferons and glatiramer acetate comparable in terms of relapse rate reduction and disease and disability progression.[6,8,10-11] Lower dosed interferon products may be more tolerable for some patients but may be associated with a reduced efficacy. Moreover, while the use of interferons or glatiramer acetate therapy may be considered in patients with progressive forms of the disease, safety and efficacy have not been established in this patient population. In addition, the development of neutralizing antibodies (NAbs) to interferons (more commonly seen with interferon beta-1b compared to interferon beta-1a therapy) may lead to a decreased efficacy of these agents.[12-13] However, the long-term impact of NAbs on clinical outcomes has not been fully determined. Therefore, at this time consensus guidelines do not recommend a change of therapy in patients positive for NAbs who are responding to interferon therapy.[10-13] Of note, NAbs disappear with continued treatment in the majority of patients. Generally, patients treated with either interferon or glatiramer acetate therapy experience a 30% reduction in relapse rate.[11] However, many patients do not optimally respond to the initial biologic response modifier therapy.[14-15] Clinical data suggests that a change of therapy may be considered in patients experiencing a suboptimal response or intolerable adverse effects. In studies, patients switching from interferon to glatiramer acetate therapy and vice versa, due to poor response, achieved a significant reduction in relapse rate and a delay in disease and disability progression.[14,16-17]

Natalizumab (Tysabri®) and mitoxantrone (Novantrone®) are also FDA approved for the treatment of RRMS. However these agents are not recommended for first-line use due to safety concerns with progressive multifocal leukoencephalopathy (PML) and cardiotoxicity, respectively.[18-19] Natalizumab is reserved for patients with rapidly advancing disease who have failed other therapies and can only be obtained through a restricted access program.[8,18] This document encompasses a review of the first-line self-administered MS biologic response modifiers.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Glatiramer acetate (Copaxone®)	Biological Response Modifiers	-
Interferon beta-1b (Betaseron®)	Biological Response Modifiers	-
Interferon beta-1a (Rebif®)	Biological Response Modifiers	-
Interferon beta-1a (Avonex®, Avonex Administration Pack®)	Biological Response Modifiers	-

Indications

All biologic response modifiers are Food and Drug Administration (FDA) approved for the treatment of relapsing-remitting Multiple Sclerosis (MS) while only Betaseron® and Avonex® are FDA approved for the treatment of first clinical episode with magnetic resonance imaging features consistent with MS.[1-4] Efficacy of biologic response modifiers in patients with chronic progressive MS has not been established.

Table 2. Food and Drug Administration Approved Indications[1-4]

Generic Name (Trade name)	Relapsing-Remitting Multiple Sclerosis	Treatment of First Clinical Episode with Magnetic Resonance Imaging Features Consistent With Multiple Sclerosis
Glatiramer acetate (Copaxone®)	✔	
Interferon beta-1b (Betaseron®)	✔	✔
Interferon beta-1a (Rebif®)	✔	
Interferon beta-1a (Avonex®)	✔	✔

Potential off-label uses may include secondary progressive multiple sclerosis (MS) with relapses.

Pharmacokinetics

Table 3. Pharmacokinetics[1-4,6]

Generic Name (Trade name)	Onset (hours)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Glatiramer acetate (Copaxone®)	Not reported	Not reported	Not reported	Not reported	Not reported
Interferon beta-1b (Betaseron®)	1-8	50	Not reported	Not reported	0.13-4.3
Interferon beta-1a (Rebif®)	16	Not reported	Not reported	Not reported	69
Interferon beta-1a (Avonex®)	3-15	Not reported	Not reported	Not reported	10

Clinical Trials

Numerous clinical studies have established the safety and efficacy of these agents in reducing the frequency of relapses and delaying disease progression and disability.[11,20-52] Moreover, there is substantial evidence of benefit in using biologic response modifiers in patients with clinically isolated syndrome (CIS). A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of converting to a clinically definite Multiple Sclerosis (CDMS) with interferon therapy compared to placebo (P<0.0001).[48] However, the evidence supporting the use of glatiramer acetate in patients with CIS is limited. In addition, the role of Multiple Sclerosis (MS) biological response modifiers in the treatment of primary or secondary progressive MS has not been determined. A recent PROMISE study failed to show a benefit of glatiramer acetate therapy in patients with primary progressive MS.[54] Several interferon studies yielded conflicting results.[55] None of the available MS biological response modifiers are Food and Drug Administration (FDA)-approved for the treatment of progressive MS.

Numerous head-to-head studies have found glatiramer acetate, interferon beta-1a administered subcutaneously (SC), and interferon beta-1b to be comparable in terms of relapse rate reduction and disease and disability progression.[23-24,26-27] However, the results of several studies suggest that lower interferon beta-1a strengths may be less efficacious while being more tolerable compared to higher dose interferons or glatiramer acetate.[30-31,34-40] A meta-analysis of six placebo-controlled studies failed to find a significant advantage of interferon beta-1a administered intramuscularly (IM) versus placebo in the number of relapse-free patients after one year of therapy.[49] In contrast, other studies found interferon beta-1a IM to be comparable to the other interferon products in terms of relapse rate reduction, disability progression and secondary progressive MS development.[32,42-46] Moreover, interferon therapy, especially the higher dose products, are associated with the production of neutralizing antibodies (NAbs) which may result in decreased radiographic and clinical effectiveness of treatment.[12-13] Exploratory post-hoc analyses of the PRISMS study linked the development of NAbs with reduced efficacy.[53] Development of NAbs among patients (N=368) randomized to receive interferon beta-1a 44 or 22 µg SC three times weekly for 4 years was associated with higher relapse rates (adjusted relapse rate ratio=1.41; 95% CI, 1.12 to 1.78; P=0.004) and a greater number of active lesions and percentage change in T2 lesion burden from baseline on magnetic resonance imaging scan (P<0.001).

It is estimated that within a few years of use, at least 30% and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively.[14,15] According to several observational studies, switching patients who have failed to adequately respond on initial treatment, to another first-line therapy is safe and effective.[16,17,47] Patients switching to glatiramer acetate after experiencing inadequate response on interferon therapy experienced a reduction in relapse rates and disability progression. Likewise, switching to interferon therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in one study.[47] The smallest reduction in the

annualized relapse rate was seen in patients who had switched from one interferon preparation to another.

Two cost-effectiveness studies evaluating glatiramer acetate and interferon therapy in patients with relapsing-remitting Multiple Sclerosis (RRMS) have been conducted in the United States.[50-51] Both studies found glatiramer acetate to be the most cost-effective biological response modifier for MS.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Boneschi et al[20] GA 20 mg SC daily vs placebo	MA Randomized, double-blind, placebo-controlled studies with patients 18-50 years of age diagnosed as having clinically definite MS with relapsing remitting course for at least one year with at least 1 relapse in the previous two years	N=540 (3 studies) Up to 35 months	Primary: Annualized relapse rate Secondary: Total number of relapses, time to first relapse, disability progression	Primary: GA therapy was associated with a statistically significant 28% reduction in the annualized relapse rate compared to placebo (0.82 vs 1.14; *P*=0.004). Secondary: GA therapy was associated with a statistically significant 36% reduction in the total number of relapses compared to placebo (*P*<0.0001). GA therapy was associated with a statistically significant 32% delay in the time to first relapse compared to placebo (322 days vs 219 days; *P*=0.01). A beneficial effect on disability progression was observed with GA therapy compared to placebo (RR, 0.6; 95% CI, 0.4 to 0.9; *P*=0.02).
Miller et al[21] GA 20 mg SC daily	OL, PRO Patients with RRMS	N=46 Up to 22 years	Primary: Annualized relapse rate, percentage of relapse-free patients, change in EDSS, adverse events Secondary: Not reported	Primary: Throughout the course of the study patients experienced a statistically significant reduction in the annualized rate of relapse from 2.9 to 0.1 at last observation (*P*<0.0001). Of patients who continued therapy through the end of the study 72% were free of relapses (*P* value not reported). There was no significant change in the mean EDSS scores from baseline (*P*=0.076) with the majority (67%) of continuing patients exhibiting improved or stable EDSS scores. The most commonly reported adverse events were injection site reactions. Six patients who received GA for up to 22 years reported lipoatrophy. Skin necrosis was not observed. A discontinuation rate of 61% was observed. The most common reason for discontinuing the study was withdrawal of consent. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Carmona et al[22] IFNb-1b (Betaseron®) 0.25 mg SC every other day vs no treatment	OL, PRO Patients with clinically definite RRSS and a history of at least two relapses in the previous 2 years	N=159 Up to 5 years	Primary: Percentage of relapse-free patients, annualized relapse rate, time to first relapse, disability progression (assessed by change in EDSS scores), time to progression Secondary: Not reported	Primary: The percentage of patients treated with IFNb-1b who were relapse-free at the end of follow-up was 21.7% (*P* value not reported). At two years of follow-up, 32.5% of patients in the IFNb-1b treated group were relapse-free compared to 22.7% in the control group (*P*=NS). The mean annualized relapse rate in the IFNb-1b treated group was 0.70 relapses per year (*P* value not reported). The mean annualized relapse rate at 2 year follow-up in the IFNb-1b treated group was 0.74 compared to 2.20 in the control group (*P*=0.001). The median time to first relapse in the IFNb-1b treated group was 375 days compared to 313 days in the control group (*P*=0.26). The mean number of relapses after 2 years of treatment decreased by 47% (from 3.2 at baseline to 1.7; *P* value not reported). At 59 months of follow-up, 25% of IFNb-1b treated patients progressed by 1 point on the EDSS from baseline (*P* value not reported). The mean time that it took for the IFNb-1b treated patients to progress by 1 point on the EDSS was longer compared to the control group (72.940 months vs 36.944 months; *P*=0.002). Higher EDSS scores were observed at the end of follow-up among patients who had experienced a relapse during the first 12 months of treatment compared to those patients who did not have a relapse (3.37 vs 2.36; *P*=0.003). At the end of follow-up, 70% of patients remained on IFNb-1b therapy with sustained efficacy and good tolerance. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
PRISMS study group[23] IFNb-1a (Rebif®) 22 µg SC three times weekly for 2 years vs IFNb-1a (Rebif®) 44 µg SC three times weekly for 2 years vs placebo for 2 years	DB, I, MC, PC, RCT Adult patients, median age 34.9 years, with RRMS and EDSS scores 0-5 and at least 2 relapses in the preceding 2 years	N=560 2 years	Primary: Mean number of relapses Secondary: Relapse rate, percentage of patients relapse-free at 1 and 2 years, mean number of moderate-severe relapses, mean number of hospital admissions, mean change in EDSS, median time to first relapse, time to sustained progression, burden of disease, adverse events	Primary: Patients randomized to IFNb-1a 22 and 44 µg treatment groups experienced significantly fewer mean number of relapses compared to patients receiving placebo at 2 years of therapy (1.82 vs 1.73 vs 2.56; *P*<0.005). Secondary: Compared to placebo, the relapse rate was reduced by 29% in the IFNb-1a 22 µg group and 32% in the IFNb-1a 44 µg treatment group (*P* value not reported). At one year, a significantly greater percentage of patients in the IFNb-1a 22 and 44 µg treatment groups were relapse-free compared to those receiving placebo (37% vs 45% vs 22%; *P*<0.005). At two years, a significantly greater percentage of patients in the IFNb-1a 22 µg (27% vs 16%; *P*≤0.05) and IFNb-1a 44 µg (32% vs 16%; *P*<0.005) treatment groups were relapse-free compared to those receiving placebo. The mean number of moderate-severe relapses was significantly lower in the IFNb-1a 22 and 44 µg treatment groups compared to placebo (0.71% vs 0.62% vs 0.99%; *P*<0.005). The mean number of hospital admissions was significantly lower in the IFNb-1a 44 µg group compared to patients receiving placebo (0.25 vs 0.48; *P*<0.005). The mean change in EDSS was significantly smaller in the IFNb-1a 22 and 44 µg groups compared to patients receiving placebo (0.23 vs 0.24 vs 0.48; *P*≤0.05). The median time to first relapse was delayed by 3 and 5 months in the IFNb-1a 22 and 44 µg groups, respectively (*P* value not reported). The time to sustained progression was significantly longer in both the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				IFNb-1a 22 and 44 µg groups compared to placebo (*P*<0.05). The burden of disease was significantly increased in the placebo group compared with the IFNb-1a 22 and 44 µg treatment groups (10.9% vs -1.2% vs -3.8%; *P*<0.0001). Of the reported adverse effects with IFNb-1a therapy, the following occurred at a greater frequency than placebo: injection-site reactions, lymphopenia, increased alanine aminotransferase, leucopenia and granulocytopenia (*P*≤0.05).
Kappos et al[24] PRISMS IFNb-1a (Rebif®) 22 µg SC three times weekly for up to 8 years vs IFNb-1a (Rebif®) 44 µg SC three times weekly for up to 8 years vs placebo for 2 years, followed by IFNb-1a 22 or 44 µg (Rebif®) SC three times a week for additional 6 years (later treatment group)	ES This was a PRISMS extension study; patients with RRMS and EDSS scores 0-5 and at least 2 relapses within 2 years prior to study onset	N=382 Up to 8 years	Primary: Mean change in EDSS scores, progression to SPMS, annualized relapse rate, percentage of relapse-free patients, annualized change in T2 BOD, change in brain parenchymal volume, adverse events, antibody development Secondary: Not reported	Primary: Among patients returning for follow-up after 8 years of therapy, mean EDSS scores increased by 1.1 point. Approximately 31.3% of patients progressed by 2 EDSS points. The longest time to reach disability progression was observed among patients initially randomized to IFNb-1a 44 µg (2.3 years vs 1 year for the late treatment group). Progression to SPMS occurred in 19.7% of patients. The time to developing SPMS was 5.3 years. The annualized relapse rate was lower in the IFNb-1a 44 µg (0.60 vs 0.78; *P*=0.014) and IFNb-1a 22 µg (0.63 vs 0.78; *P*<0.001) treatment groups compared to the late treatment group. The greatest percentage of patients remaining relapse-free at follow-up were those receiving IFNb-1a 44 µg therapy (15.4%) compared to patients in the IFNb-1a 22 µg (8.1%) and late treatment groups (6.5%; *P* value not reported). Compared to the late treatment group, patients initially randomized to IFNb-1a 44 µg therapy had a lower increase in T2 BOD (24.5% vs 5.0%; *P*=0.002). At two years of follow-up, patients receiving placebo experienced a greater median annualized increase in T2 BOD compared with the IFNb-1a 22 and 44 µg treatment groups (6.5% vs -0.7% vs -2.8%; *P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). At 8-year follow-up, all treatment groups experienced a median relative reduction in brain parenchymal volume of 3.9% from baseline (*P* value not reported). At 8-year follow-up, the most frequently reported adverse events were application-site disorders, reported by 44% of patients. Flu-like symptoms occurred in 11.7% of patients. Elevated alanine transaminase was the most common liver abnormality, affecting approximately 8.4% of patients on IFNb-1a therapy. Lymphopenia and leukopenia were reported by 19.6% and 14% of patients receiving IFNb-1a therapy, respectively. Of patients who developed antibodies, 90% did so during the first two years of therapy. Of patients returning for follow-up after 8 years of therapy 72% remained on SC IFNb-1a. Secondary: Not reported
Coppola et al[25] IFNb-1a (Avonex®) 30 µg IM once weekly for a mean of 31.7 months	OS, PRO Patients with a clinically definite or laboratory-confirmed MS	N=255 Mean of 31.7 months	Primary: Percentage of patients progression-free, percentage of patients relapse-free, relapse rate, change in EDSS scores, estimated time to disability progression Secondary: Not reported	Primary: At 3 years of therapy 58% of patients remained progression-free (*P* value not reported). At 3 years of therapy 39.6% of patients remained relapse-free (*P* value not reported). At 3 years of therapy 88% of patients had an improved relapse rate compared to baseline (*P* value not reported). After 3 years of therapy, mean EDSS scores increased by 0.4 points from baseline (*P* value not reported). The estimated median time to disability progression among patients

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				receiving IFNb-1a therapy was 4.5 years (*P* value not reported). Within the 3-year follow-up period 31% of patients discontinued the study. Reasons for discontinuation were disease activity (66%), voluntary decision (23%) and adverse events (11%). Secondary: Not reported
Flechter et al[26] GA 20 mg SC once daily vs GA 20 mg SC every other day vs IFNb-1b (Betaseron®) 0.25 mg SC every other day	OL, PRO Patients ≥18 years of age, with clinically definite MS and at least 2 exacerbations within the previous 2 years	N=58 2 years	Primary: Relapse rate, change in EDSS score, adverse effects Secondary: Not reported	Primary: At 1 and 2 years of follow-up, the relapse rate decreased significantly in all three treatment groups from 1 and 2 years prior to study onset, respectively (*P*<0.05). While there was no significant changes in the EDSS scores from baseline at 2 years of follow-up in the IFNb-1b group (*P*=0.3), patients receiving GA daily or every other day experienced significantly higher EDSS scores from baseline (*P*=0.007, *P*=0.04, respectively). There was no statistically significant difference in side effects among the three treatment groups (*P*=NS). IFNb-1b groups reported the following adverse effects: flu-like symptoms, increased spasticity, injection-site reactions and systemic reactions. GA daily group experienced the following adverse effects: flu-like symptoms, injection-site reactions, systemic reaction, lymphadenopathy and lipodystrophy. Side effects were generally reported within the first 6 months of therapy and resolved with continue d therapy. Secondary: Not reported
Mikol et al[27] REGARD	MC, OL, PG, RCT Patients between 18 and 60 years of age,	N=764 96 weeks	Primary: Time to first relapse (defined as new or worsening	Primary: There was no statistically significant difference in the primary endpoint between the IFNb-1a and GA groups (HR, 0.94; 95% CI, 0.74 to 1.21; *P*=0.64).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GA 20 mg SC once daily for 96 weeks vs IFNb-1a (Rebif®) 44 µg SC three times weekly for 96 weeks	naïve to either of the study drugs, diagnosed with RRMS with the McDonald criteria, with an EDSS score of 0-5.5, at least one attack within past 12 months and clinically stable or neurologically improving during the 4 weeks before study onset		neurological symptoms, without fever, lasting at least 48 hours and accompanied by a change in KFS score) Secondary: Proportion of patients relapse-free over study period, relapse rate, number of active T2 lesions (defined as new or enlarging per patient per scan over 96 weeks), mean number of gadolinium-enhancing lesions/patient/scan, change in the volume of gadolinium-enhancing lesions, change in T2 volume, CUA lesions, new T1 hypointensities, T1 hypointense lesion volume, brain volume, disability progression, adverse effects	Secondary: There was no statistically significant difference between the groups in the proportion of patients who were free from relapse over study period (*P*=0.96). There was no statistically significant difference between the groups in the annualized relapse rate over the study period (*P*=0.828). There was no statistically significant difference between the groups in the number of active T2 lesions (new or enlarging) per patient per scan over 96 weeks of therapy (*P*=0.18). There was no statistically significant difference between the groups in mean change in T2 lesion volume over 96 weeks of therapy (*P*=0.26). Patients randomized to IFNb-1a experienced a significantly lower number of gadolinium-enhancing lesions per patient per scan compared to the glatiramer-treated group (0.24 vs 0.41; *P*=0.0002). Over the 96 weeks of therapy, a significantly greater number of patients randomized to IFNb-1a were free of gadolinium-enhancing lesions compared to the glatiramer-treated groups (81% vs 67%; *P*=0.0005). There was no statistically significant difference between the groups in mean change in gadolinium-enhancing lesion volume over 96 weeks of therapy (*P*=0.42). Patients randomized to IFNb-1a experienced a significantly lower number of CUA lesions per patient per scan compared to the glatiramer-treated group (0.91 vs 1.22; *P*=0.01). There was no statistically significant difference between the groups in the number of new T1 hypointense lesions per patient per scan over 96 weeks of therapy (*P*=0.15).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference between the groups in mean change in new T1 hypointense lesion volume over 96 weeks of therapy (*P*=0.29). There was a significant reduction in brain volume among patients randomized to IFNb-1a compared to the glatiramer-treated group (*P*=0.018). There was no significant difference between the IFNb-1a and glatiramer groups in the proportion of patients with a 6-month confirmed EDSS progression (11.7% vs 8.7%; *P*=0.117) Patients randomized to IFNb-1a and glatiramer therapies experienced 632 and 618 treatment-related adverse effects, respectively (*P* value not reported). Treatment-related adverse effects occurring significantly more often in the IFNb-1a group than in the glatiramer group included influenza-like illness, headache, myalgia and increased alanine aminotransferase (*P*<0.05). Treatment-related adverse effects occurring significantly more often in the GA group than in the IFNb-1a group included pruritis, swelling, induration at the injection site, dyspnea and post-injection systemic reactions (*P*<0.05).
Koch-Henriksen et al[28] IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Rebif®) 22 µg SC once weekly	MC, OL, RCT Patients with RMSS, ≥2 relapses within 2 years, EDSS score of ≤5.5	N=421 24 months	Primary: Annualized relapse rate, time to first relapse, neutralizing antibody formation Secondary: Time to sustained progression	Primary: Annual relapse rates, time to first relapse and neutralizing antibody formation were similar in both treatment arms (*P*=NS). Secondary: Time to sustained progression similar in both treatment arms (*P*=NS). Other: Side effects (15%) were the most frequent cause of withdrawal in the IFNb-1b group and treatment failure was the most frequent cause of withdrawal in the IFNb-1a group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Baum et al[29] BRIGHT IFNb-1b (Betaseron®) 250 µg SC every other day vs IFNb-1a (Rebif®) 44 µg SC three times weekly	I, MC, OS, PRO Patients, mean age 36 years, diagnosed with RRMS and treated with either one of the study regimens	N=445 15 consecutive injections (follow-up period, 4-5 weeks)	Primary: The proportion of patients pain-free during all injections (immediately, 30 minutes and 60 minutes post injection) Secondary: Proportion of injections that were pain free per patient, the mean VAS per patient, impact of injection-site pain on comfort and satisfaction with treatment	Primary: A significantly greater proportion of patients receiving IFNb-1b compared to IFNb-1a were free from pain immediately, 30 minutes and 60 minutes after injection (*P*<0.0001 at all time points). Secondary: The proportion of pain-free injections per patient was significantly greater with IFNb-1b compared to IFNb-1a immediately, 30 minutes and 60 minutes after injection (*P*<0.0001 at all time points). Mean VAS scores per patient were significantly lower with IFNb-1b compared to IFNb-1a immediately, 30 minutes and 60 minutes after injection (*P*<0.0001 at all time points). Injection-site reactions occurred in a significantly lower proportion of patients who were treated with IFNb-1b vs IFNb-1a (*P*<0.05). A significantly greater proportion of patients treated with IFNb-1a compared with IFNb-1b reported that pain after injection negatively impacted their satisfaction with treatment (35.9% vs 23.1%; *P*=0.006). Adverse effects were reported by 33.3% of patients treated with IFNb-1b compared with 32.4% of patients receiving IFNb-1a therapy (*P* value not reported).
Barbero et al[30] INCOMIN IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Avonex®) 30 µg IM once weekly	MC, PG, PRO, RCT IFNb-naïve patients with RRMS, ≥2 exacerbations in prior 2 years, EDSS scores of 1 to 3.5	N=188 2 years	Primary: Proportion of patients with ≥1 active MRI lesion Secondary: Total area/volume of brain lesions or BOD, correlation between primary outcome and NAb status	Primary: Significantly fewer patients had ≥1 active lesion in the IFNb-1b arm than in the IFNb-1a arm (17% vs 34%; *P*<0.014). Secondary: The mean T2 BOD showed a progressive decrease from baseline in patients treated with IFNb-1b and a progressive increase in patients treated with IFNb-1a (*P*<0.001). NAb did not appear to have any impact on changes in MRI activity associated with IFNb-1b treatment during the entire study period (*P*=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Durelli et al[31] INCOMIN IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Avonex®) 30 µg IM once weekly	MC, PG, PRO, RCT IFN-naïve patients with RRMS, ≥2 exacerbations in prior 2 years, EDSS scores of 1 to 3.5	N=188 2 years	Primary: Proportion of patients free from relapses Secondary: Annualized relapse rate, annualized treated relapse rate, proportion of patients free from sustained and confirmed progression in disability, EDSS score and time to sustained and confirmed progression in disability	Primary: Fifty-one percent of patients taking IFNb-1b remained relapse-free while 36% of patients taking IFNb-1a remained relapse-free (*P*=0.03). Secondary: IFNb-1b treatment resulted in fewer relapses per patient (0.5 vs 0.7; *P*=0.03), fewer treated relapses (0.38 vs 0.50; *P*=0.09), lower EDSS scores (2.1 vs 2.5; *P*=0.004), lower proportion of patients with progression in EDSS score of 1 point sustained for 6 months and confirmed at end of study (13% vs 30%; *P*=0.005) and longer time to sustained and confirmed disability progression (*P*<0.01) than IFNb-1a treatment. Most adverse events (flu-like syndrome, fever, fatigue, increased liver enzymes) declined following 6 months of treatment. The frequency of adverse events was similar between groups. Local skin reactions and NAb were more common in patients treated with IFNb-1b vs IFNb-1a. Neutralizing antibodies were reduced during the second year of treatment and did not appear to have any correlation with relapse rate. No *P* values were reported for adverse events.
Minagara et al[32,33] PROOF IFNb-1a (Rebif®) 44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly	DB, MC, OS, PRO, RETRO Patients between 18 and 50 years of age, with a diagnosis of RRMS and an EDSS score of 0-5.5, at least 2 documented relapses during the 3 years before study onset, receiving Avonex® 30 µg IM once weekly or Rebif® 44 µg SC three times	N=136 12-24 months (retro-spective phase) 6 month (prospective phase)	Primary: Change in BPF Secondary: Proportion of patients who experienced relapses at 6 months, annualized relapse rate, change in EDSS, NAb formation, adverse effects	Primary: There was no statistically significant difference between the groups in the change in BPF (*P* value not reported). Secondary: There was no statistically significant difference between the groups in the rate of relapse (*P* value not reported). There was no statistically significant difference between the groups in the change in EDSS scores, suggesting similar sustained disability progression in both the IM IFNb-1a and SC IFNb-1a groups (25.8% vs 26.7%; *P* value not reported). More patients in the SC IFNb-1a group developed NAbs compared to the IM IFNb-1a group (19% vs 0%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	weekly for at least 12 months and up to 24 months before enrollment			More patients positive for NAb compared to those negative for NAb had disability progression (40.0% vs 27.8%; *P*>0.05), new or enlarging T2 lesions (63.6% vs 40.7%; *P*=0.003) and gadolinium-enhancing lesions after 12-24 months of therapy (36.4% vs 15.0%; *P*=0.001). While general tolerability was comparable between the study drugs, SC IFNb-1a was associated with a greater incidence of injection-site reactions compared to the IM formulation (6.0% vs 2.9%; *P* value not reported).
Panitch et al[34] EVIDENCE IFNb-1a (Rebif®) 44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly	MC, PG, RCT IFNb-naïve patients with RRMS, ≥2 exacerbations in prior 2 years, EDSS scores of 0 to 5.5	N=677 48 weeks	Primary: Proportion of patients who were relapse-free at 24 weeks Secondary: Relapse rate, time to first relapse, number of active lesions per patient per scan on MRI	Primary: More patients in the 44 than the 30 µg group remained relapse free at 24 weeks (75% vs 63%; *P*=0.0005) and at 48 weeks (62% vs 52%; *P*=0.009). Secondary: The time to first relapse was prolonged in the 44 µg group compared with the 30 µg group (*P*=0.003). Patients receiving 44 µg compared with 30 µg had fewer active MRI lesions (*P*<0.001). Injection-site reactions, asymptomatic abnormalities of liver enzymes, and altered leukocyte counts were more frequent with 44 µg compared with 30 µg (83% vs 28%; *P*<0.001), (18% vs 9%; *P*<0.002), and (11% vs 5%; *P*<0.003), respectively. Nab developed in 25% of the 44 µg group compared with 2% of the 30 µg group (*P*<0.001).
Panitch et al[35] EVIDENCE IFNb-1a (Rebif®) 44 µg SC three times weekly vs	MC, PG, RCT A 64-week follow-up of the EVIDENCE trial. IFNb-naïve patients with RRMS, ≥2 exacerbations in prior 2 years, EDSS scores	N=677 64 weeks	Primary: Proportion of patients who were relapse-free at 24 weeks Secondary: Relapse rate, time to first and second	Primary: At study endpoint, 56% of patients in the 44 µg group and 48% in the 30 µg group remained relapse-free (*P*=0.023). Secondary: In the 44 µg group compared with the 30 µg group, there was a 17% reduction in relapse rate, a delayed time to first relapse (HR, 0.70), and a 32% reduction in steroid use to treat relapses (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNb-1a (Avonex®) 30 µg IM once weekly	of 0 to 5.5		relapse, number of T2 active lesions per patient per scan, percentage of active scans per patient, proportion of patients with no active lesions	In the 44 µg group compared with the 30 µg group, MRI activity was decreased with reductions in T2 active lesions and proportion of active scans and increases in patients with no active scans (*P*<0.001, all). The presence of NAb was associated with reduced efficacy for MRI measures and fewer IFNb-related adverse effects, but did not have a significant impact on relapse measures.
Schwid et al[36] EVIDENCE IFNb-1a (Rebif®) 44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly increased to 44 µg SC three times weekly Patients initially randomized to 30 µg once weekly were allowed to switch to 44 µg three times a week after 48 weeks of therapy while patients initially randomized to 44 µg three times a week could withdraw from the study or continue on the regimen for an additional 8 months.	ES, MC, PB, PG, RCT An 8 month extension of the EVIDENCE trial. IFNb-naïve patients with RRMS, ≥2 exacerbations in prior 2 years, EDSS scores of 0 to 5.5	N=677 80 weeks	Primary: Change in relapse rate Secondary: Change in the number of T2 active lesions per patient per scan, proportion of T2 active scans per patient, proportion of patients without T2 active scans	Primary: The relapse rate decreased from 0.64 to 0.32 for patients changing therapy (*P*<0.001) and from 0.46 to 0.34 for patients continuing therapy (*P*=0.03). The reduction in relapse rate was greater among patients switching to a higher dose and frequency regimen (*P*=0.047). Secondary: Patients converting to the higher dose and frequency regimen had fewer active lesions on T2-weighted MRI (*P*=0.02), fewer active scans (*P*=0.01) and no significant changes in the proportion of patients without active scans (*P*=NS). There were no significant changes in the continuing therapy group (*P*=NS). Seventy-three percent of the 306 patients receiving 30 µg converted to 44 µg and 91% receiving 44 µg continued the same therapy. Patients converting to the increased dose and frequency regimen experienced a higher incidence of adverse effects.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Schwid et al[37] EVIDENCE IFNb-1a (Rebif®) 44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly, increased to 44 µg SC three times weekly Patients initially randomized to 30 µg once weekly were allowed to switch to 44 µg three times a week after 48 weeks of therapy while patients initially randomized to 44 µg three times a week could withdraw from the study or continue on the regimen for an additional 8 months.	AB, I, MC, PG, RCT, XO Full results of the EVIDENCE trial. IFNb-naïve patients, between 18 and 55 years of age, with RRMS, ≥2 exacerbations in prior 2 years, EDSS scores of 0 to 5.5	N=677 80 weeks	Primary: Proportion of patients free of relapses Secondary: Time to first relapse, annualized relapse rate, number of steroid courses, number of T2 active lesions per patient per scan, percentage of active scans per patient, proportion of patients with no active scans, adverse events, NAb detected	Primary: A significantly greater proportion of patients randomized to receive IFNb-1a 44 µg SC therapy remained free from relapses during the comparative phase of the study, compared to patients in the once weekly 30 µg IM group (56% vs 48%; OR, 1.5; 95% CI, 1.1 to 2.0; *P*=0.023). Secondary: Compared to patients in the IFNb-1a 30 µg IM group, patients in the high-dose IFNb-1a 44 µg SC group experienced a significant 30% reduction in the time to first relapse (HR, 0.70; *P*=0.002) during the comparative phase of the study. Compared to patients in the IFNb-1a 30 µg IM group, patients in the high-dose, IFNb-1a 44 µg SC group experienced a significant 17% reduction in annualized relapse rate (*P*=0.033) during the comparative phase of the study. A statistically significant 50% reduction in the mean annualized relapse rate occurred among patients who converted from IFNb-1a 30 µg IM to IFNb-1a 44 µg SC (*P*<0.001) during the crossover phase of the study. A statistically significant 26% reduction in the mean annualized relapse rate occurred among patients who continued to receive IFNb-1a 44 µg SC (*P*=0.028) during the crossover phase of the study. A significantly lower number of steroid courses per patient per year was used in the high-dose, IFNb-1a 44 µg SC group compared to the IFNb-1a 30 µg IM group (0.19 vs 0.28; *P*=0.009) during the comparative phase of the study. Patients in the IFNb-1a 44 µg SC group had a significantly fewer mean number of T2-active lesions compared to patients in the IFNb-1a 30 µg IM group (0.9 vs 1.4; *P*<0.001) during the comparative phase of the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A significant reduction in the mean number of T2-active lesions occurred among patients who converted from IFNb-1a 30 µg IM to IFNb-1a 44 µg SC during the crossover phase of the study (*P*=0.022). Patients in the IFNb-1a 44 µg SC group had a significantly lower percentage of T2-active scans per patient compared to patients in the IFNb-1a 30 µg IM group (27% vs 44%; *P*<0.001) during the comparative phase of the study. Patients who converted from IFNb-1a 30 µg IM to IFNb-1a 44 µg SC experienced a statistically significant reduction in the percentage of T2-active scans per patient during the crossover phase of the study (*P*<0.001). A significantly greater percentage of patients randomized to the IFNb-1a 44 µg SC group did not have a T2-active scan compared to patients in the IFNb-1a 30 µg IM group (58% vs 38%; OR, 2.4; 95% CI, 1.7 to 3.3; *P*<0.001) during the comparative phase of the study. Converting from IFNb-1a 30 µg IM to IFNb-1a 44 µg SC was not correlated with a significant change in the percentage of patients with no T2-active scans (*P*=0.803). Patients who continued IFNb-1a 44 µg SC therapy from the start of the study did not have significant changes in any of the MRI measures (*P* value not reported). Injection-site reactions were significantly more common in patients receiving IFNb-1a 44 µg SC than in patients on IFNb-1a 30 µg IM therapy (85% vs 33%; *P*<0.001). Flu-like symptoms were significantly more common in patients receiving IFNb-1a 30 µg IM than in patients on IFNb-1a 44 µg SC therapy (53% vs 45%; *P*=0.031). Abnormal liver function test results were significantly more common in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients receiving IFNb-1a 44 µg SC than in patients on IFNb-1a 30 µg IM therapy (18% vs 10%; *P*=0.003). Most liver enzyme elevations resolved with continued therapy. Abnormal WBC counts were significantly more common in patients receiving IFNb-1a 44 µg SC than in patients on IFNb-1a 30 µg IM therapy (14% vs 5%; *P*<0.001). WBC counts normalized in most patients with continued therapy. NAbs were detected in a significantly greater percentage of patients receiving IFNb-1a 44 µg SC compared with IFNb-1a 30 µg IM (26% vs 3%; *P*<0.001). However, relapse rate was not affected by the NAb status (*P*=0.203).
Traboulsee et al[38] EVIDENCE IFNb-1a (Rebif®) 44 µg SC three times weekly for 48 weeks vs IFNb-1a (Avonex®) 30 µg IM once weekly, increased to 44 µg SC three times weekly for 48 weeks	PH This was a post-hoc analysis of the EVIDENCE study; patients were included if had received at least one dose of the study drug and had an evaluable T2-weighted MRI scan obtained at baseline and week-48	N=533 48 weeks	Primary: Percentage change in T2 BOD from baseline to week-48 Secondary: Absolute change in BOD, percentage and absolute change in BOD when stratified by NAb status from baseline to week-48	Primary: Median percentage decreases in BOD were greater in the IFNb-1a 44 µg SC group compared to patients randomized to the IFNb-1a 30 µg IM treatment group (-6.7% vs -0.6%; *P* value not reported). The AMTD in percentage change in BOD from baseline to week-48 showed a significant treatment benefit for patients treated with IFNb-1a 44 µg SC compared to IFNb-1a 30 µg IM (-4.6%; SE, 2.6%; *P*=0.002). Secondary: A greater median absolute reduction from baseline in BOD was observed in the IFNb-1a 44 µg SC group compared with IFNb-1a 30 µg IM (-189.5 vs -19.0; *P* value not reported). Among patients randomized to IFNb-1a 44 µg SC, median percentage decreases in BOD were smaller in patients positive for NAbs compared to those with a negative NAb status (-0.8 vs -8.0; *P* value not reported). Among patients randomized to IFNb-1a 44 µg SC, absolute decreases in BOD were smaller in patients positive for NAbs compared to those with a negative NAb status (-46.2 vs -254.6; *P* value not reported). The AMTD in percentage change in BOD from baseline to week-48 showed a significant treatment benefit for NAb negative patients treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with IFNb-1a 44 µg SC compared to IFNb-1a 30 µg IM treated patients (-6.6%; SE, 2.8%; *P*<0.0001). The AMTD in percentage change in BOD from baseline to week-48 showed comparable treatment benefit for NAb positive patients treated with IFNb-1a 44 µg SC compared to IFNb-1a 30 µg IM treated patients (-0.5%; SE, 3.9%; *P*=0.583).
Khan et al[39] GA 20 mg SC daily vs IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Avonex®) 30 µg IM once weekly vs no treatment	MC, OL, PRO Patients with RRMS, ≥1 relapses in past 2 years, EDSS score ≤4	N=156 12 months	Primary: Relapse rate Secondary: Change EDSS scores, relapse rate during each half of study, proportion of relapse-free patients and proportion of relapse-free patients during each half of the study	Primary: Relapse rates were 0.97, 0.85, 0.61 and 0.62 in the no treatment, IFNb-1a, IFNb-1b and GA groups, respectively. Reduction in the relapse rate compared with no treatment was statistically significant only in the IFNb-1b (*P*<0.002) and GA (*P*<0.003) groups. Secondary: Mean EDSS scores were significantly reduced only in the IFNb-1b (*P*<0.01) and GA (*P*<0.001) groups compared with no treatment. There were no significant reductions in relapse rates in the first half of the study and only GA-treated patients displayed a significant reduction in the second half (*P*=0.004). The proportion of relapse-free patients were 15%, 20%, 39% and 38% in the no treatment, IFNb-1a, IFNb-1b and GA groups, respectively. The differences between the IFNb-1b and GA groups were statistically significant compared with placebo (*P*=0.037 and *P*=0.038, respectively). There was no significant difference between IFNb-1a and placebo (*P*=NS). Of the 156 patients, 33 elected no treatment, 40 elected IFNb-1a, 41 elected IFNb-1b and 42 elected GA.
Khan et al[40] GA 20 mg SC daily vs	MC, OL, PRO 18 months follow up study; patients with RRMS, ≥1 relapses in past 2 years, EDSS	N=156 18 months	Primary: Relapse rate Secondary: Change in EDSS scores, proportion of	Primary: Relapse rates were 1.02, 0.81, 0.55 and 0.49 in the no treatment, IFNb-1a, IFNb-1b and GA groups, respectively. Reduction in the relapse rate compared with no treatment was statistically significant only in the IFNb-1b and GA (*P*=0.001) groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Avonex®) 30 µg IM once weekly vs no treatment	score ≤4		relapse-free patients	Secondary: Mean EDSS scores were significantly reduced only in the IFNb-1b (P<0.01) and GA (P=0.003) groups compared with no treatment. The proportions of relapse-free patients were 6.7%, 11.8%, 32.4% and 33.3% in the no treatment, IFNb-1a, IFNb-1b and GA groups, respectively. A significantly greater proportion of patients in the IFNb-1b and GA groups were relapse-free over 18 months of follow-up compared with the no treatment group (P=0.05). There was no significant difference in the proportion of relapse-free patients between IFNb-1a and the no treatment group (P>0.999).
Etemadifar et al[41] IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Rebif®) 44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly	MC, RCT, SB Patients with RRMS, ≥2 relapses in past 2 years, EDSS score ≤5	N=90 24 months	Primary: Number of relapses, proportion of relapse-free patients, EDSS scores Secondary: Not reported	Primary: Mean relapse rates were reduced from 2.0 to 1.2, 2.4 to 0.6 and 2.2 to 0.7 episodes (P<0.001 for each) for IFNb-1a 30 µg, IFNb-1a 44 µg, and IFNb-1b, respectively. The proportion of relapse-free patients were 20%, 43% and 57% for IFNb-1a 30 µg, IFNb-1a 44 µg, and IFNb-1b, respectively. The mean number of relapses were lower with IFNb-1a 44 µg and IFNb-1b than with IFNb-1a 30 µg therapy (P<0.05). EDSS scores decreased by 0.3 in the IFNb-1a 44 µg group (P<0.05) and 0.7 in the IFNb-1b group (P<0.001) while the IFNb-1a 30 µg group remained stable. Secondary: Not reported
Rio et al[42] IFNb-1b (Betaseron®) 0.25 mg SC every other day vs	OL, OS, PM Patients with RRMS, active disease with ≥2 relapses in the previous 2 years, EDSS score between 0 and 5.5	N=495 Up to 8 years	Primary: Proportion of relapse-free patients, proportion of patients with confirmed and sustained disability progression,	Primary: At 2 years 59%, 59% and 50% were relapse-free in the IFNb-1a 30 µg, IFNb-1a 22 µg, and IFNb-1b groups, respectively. At 4 years 52%, 39% and 35% were relapse-free in the IFNb-1a 30 µg, IFNb-1a 22 µg and IFNb-1b groups, respectively. Each group showed a significant reduction in relapse rate (P<0.0001). The number of relapses decreased with treatment at 2 years (2.24 to 0.80 for IFNb-1a 30 µg), (2.51 to 0.64 for IFNb-1a 22 µg), and (2.86 to 0.87 for IFNb-1b). The relapse rates

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNb-1a (Rebif®) 22 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly			annualized relapse rate, proportion of decrease in relapse rate, proportion of patients reaching EDSS of 6, number of patients who discontinued treatment due to inefficacy Secondary: Not reported	decreased at 4 years (1.07 to 0.33 for IFNb-1a 30 µg; *P*<0.0001), (1.21 to 0.41 for IFNb-1a 22 µg; *P*<0.0001), and (1.36 to 0.38 for IFNb-1b; *P*<0.0001). The proportions of patients with confirmed and sustained disability at 2 and 4 years were 17% and 23% for IFNb-1a 30 µg, 19% and 35% for IFNb-1a 22 µg, and 10% and 24% for IFNb-1b, respectively. There were no significant differences between groups (*P*=NS). Thirteen percent of patients had an EDSS ≥6 following 4 years of therapy. There were no significant differences between groups (*P*=NS). The proportions of patients discontinuing treatment due to inefficacy were 8% for IFNb-1a 30 µg, 3% for IFNb-1a 22 µg and 10% for IFNb-1b (*P* values were not reported). Patients selecting IFNb-1a 30 µg were older than those selecting IFNb-1a 22 µg. Patients selecting IFNb-1b had greater disease activity and disability at baseline compared to the other treatments. Secondary: Not reported
Trojano et al[43] IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Rebif®) 22 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly	MC, OL, OS, PM Patients with RRMS	N=1,033 24 months	Primary: Proportion of relapse-free patients, number of patients with a ≥1.0 point progression in EDSS Secondary: Changes from baseline in annualized relapse rate and EDSS score	Primary: The proportions of patients who were relapse free in each group were similar (54% with IFNb-1a 30 µg, 49% with IFNb-1a 22 µg and 54% with IFNb-1b at 12 months *(P* value not reported). The proportions of patients who remained relapse free at 24 months were 33% with IFNb-1a 30 µg and 38% with IFNb-1b (*P*=NS). The numbers of patients with a ≥1.0 point progression in EDSS were similar (3% with IFNb-1a 30 µg, 5% with IFNb-1a 22 µg and 4% with IFNb-1b at 12 months (*P*=NS) The numbers of patients with a ≥1.0 point progression in EDSS at 24 months were 7% with IFNb-1a 30 µg and 11% with IFNb-1b (*P*=NS). Secondary: Relapse rates were 0.71 with IFNb-1a 30 µg and 0.65 with IFNb-1b

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P*=0.16). Mean changes in EDSS score were similar among the groups (*P*=NS).
Trojano et al[44] IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Rebif®) 22 µg SC three times weekly vs IFNb-1a (Rebif®) 44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly vs no treatment	OS Patients with RRMS	N=1,504 7 years	Primary: Incidence of SPMS Secondary: EDSS score of 4, EDSS score of 6	Primary: The IFNb-treated patients showed a reduction in the incidence of SPMS compared with untreated patients (*P*<0.0001) in terms of time from first visit (HR, 0.38) and current age (HR, 0.36). Secondary: There was a significant difference in favor of IFNb-treated patients for EDSS score of 4 (*P*<0.02) and EDSS score of 6 (*P*≤0.03).
Limmroth et al[45] QUASIMS IFNb-1b (Betaseron®) 250 µg SC every other day for up to 2 years vs	MC, OS Patients 18-65 years of age with RRMS and uninterrupted ≥2 year history of therapy with one of the study regimens	N=4,754 ≥2 years	Primary: Change from baseline EDSS score, percentage of progression-free patients (defined as <1.0 point increase in EDSS score over 2 years of therapy), percentage of	Primary: There were no differences in the change from baseline EDSS scores among treatment naïve patients who received IFNb-1a 30 µg, IFNb-1b, IFNb-1a 22 µg and IFNb-1a 44 µg regimens over 2 years of therapy (0.17 vs 0.25 vs 0.20 vs 0.35, respectively; *P* value not reported). The percentage of progression-free patients was significantly lower in the IFNb-1a 44 µg group compared with the IFNb-1a 30 µg group (*P*<0.001) and IFNb-1a 22 µg group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNb-1a (Rebif®) 22 µg SC three times weekly for up to 2 years vs IFNb-1a (Rebif®) 44 µg SC three times weekly for up to 2 years vs IFNb-1a (Avonex®) 30 µg IM once weekly for up to 2 years			relapse-free patients, annualized relapse rate, reasons for therapy change Secondary: Not reported	The percentage of progression-free patients was significantly lower in the IFNb-1b group compared with the IFNb-1a 30 µg group (*P*=0.001). The percentage of relapse-free, treatment-naïve patients was significantly lower in the IFNb-1a 44 µg group compared with the IFNb-1a 30 µg group (34.6% vs 48.5%; *P*=0.002) and IFNb-1b group (34.6% vs 45.7%; *P*=0.007). The percentage of relapse-free, treatment-naïve patients was significantly lower in the IFNb-1a 22 µg group compared with the IFNb-1a 30 µg group (39.8% vs 48.5%; *P*=0.005). There were no statistically significant differences in the annualized relapse rate over 2 years among treatment-naïve patients who received IFNb-1a 30 µg, IFNb-1b, IFNb-1a 22 µg and IFNb-1a 44 µg regimens (0.51 vs 0.52 vs 0.53 vs 0.63, respectively; *P*=NS). The most common reason for therapy change was a perceived lack of efficacy (7.1%). A significantly greater percentage of patients changed therapy due to perceived lack of efficacy in the IFNb-1a 22 µg group compared to either IFNb-1a 30 µg (*P*=0.0027) or IFNb-1b group (*P*<0.0001). Therapy change due to injection-site reactions was significantly less frequent among patients receiving IFNb-1a 30 µg compared with IFNb-1b (*P*<0.0001) and IFNb-1a 22 µg groups (*P*=0.0001). In addition, a significantly greater percentage of patients in the IFNb-1b group changed therapy due to flu-like symptoms compared to patients in the IFNb-1a 22 µg group (1.2% vs 0.2 %; *P*=0.0038). Secondary: Not reported
Haas et al[46] GA 20 mg SC weekly	OL, RETRO Patients with RRMS, 1-3 exacerbations	N=308 24 months	Primary: Relapse rate Secondary:	Primary: The relapse rates decreased significantly for all drugs (*P*<0.05), with values of 0.80, 0.69, 0.66 and 0.36 for IFNb-1a 30 µg, IFNb-1b, IFNb-1a 22 µg and GA, respectively. There were no significant differences

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Rebif®) 22 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly	within previous year, EDSS score ≤3.5		Number of relapse-free patients, mean EDSS change and progression rate	between the groups at 6 months, but the decline in relapse rate at 24 months was highest with GA (0.81; *P*<0.001). Secondary: The percentage of relapse-free patients at 24 months was 35.4%, 45.5%, 45.8% and 58.2% for IFNb-1a 30 µg, IFNb-1b, IFNb-1a 22 µg and GA, respectively (*P*=NS). There were no significant differences in EDSS between groups (*P*=NS). The progression index declined in all treatment groups (*P* values were not reported). The discontinuation rate between 6 and 24 months was highest for IFNb-1a 30 µg and lowest for GA (33% vs 9%; *P*<0.001).
Caon et al[16] GA 20 mg SC daily administered for up to 42 months to patients who had previously received IFNb-1a 30 µg IM once weekly therapy for up to 24 months	OL, PRO Patients 18 years of age or older with RRMS	N=85 Up to 24 months	Primary: Annualized relapse rate Secondary: Change in EDSS	Primary: Switching to GA therapy was associated with a statistically significant 57% reduction in the annualized relapse rate from 1.23 to 0.53 (*P*=0.0001). In a subgroup of patients who switched to GA due to lack of efficacy with IFNb-1a, the annualized relapse rate was reduced from 1.32 to 0.52 (61%; *P*=0.0001). There was no statistically significant reduction in the annualized relapse rate among patients who switched from IFNb-1a to GA therapy due to adverse effects (*P*=NS). Secondary: After 37.5 months of GA therapy there was a statistically significant improvement in mean EDSS scores (*P*=0.0001).
Zwibel et al[17] GA 20 mg SC daily administered to treatment naive patients	MC, OL, PRO Patients 18 years of age or older with RRMS, EDSS	N=805 3.5 years	Primary: Annual relapse rate, proportion of relapse-free patients, time to first	Primary: There was no statistically significant difference between the prior IFNb-1b and treatment-naïve groups in the reduction of annualized relapse rate from 2 years before study entry (75% in both groups; *P*=0.148).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs GA 20 mg SC daily administered to patients who had previously received IFNb-1b therapy	disability score ≤6		relapse, progression of neurological disability (measured by change in EDSS score from baseline), proportion of patients with sustained progression (≥1 EDSS point increase for 6 months) Secondary: Not reported	There was no statistically significant difference between the prior IFNb-1b and treatment-naïve groups in the proportion of relapse-free patients throughout the study (68.4% vs 69.5%; *P*>0.9). Estimated times to first relapse for 25% of patients in the prior IFNb-1b and treatment-naïve groups were 245 days and 328 days, respectively (*P*=0.28). Patients with a prior history of IFNb-1b therapy exhibited a higher rate of neurological disability progression at 12 and 18-months and last observation compared to treatment-naïve patients (*P*=0.0070, *P*=0.0155, *P*=0.0018, respectively). There were no statistical differences between the study groups in the proportion of patients with sustained progression (*P*=0.209). Secondary: Not reported
Carra et al[47] GA 20 mg SC weekly for 3 years, subsequently switched to IFNb or mitoxantrone* therapy for additional 3 years vs IFNb-1b (Betaseron®) 0.25 mg SC every other day for 3 years, subsequently switched to GA or mitoxantrone* therapy for additional 3 years	MC, OS, PRO Patients 18 years of age or older with RRMS, EDSS disability score <6, ≥1 relapse in the previous year	N=114 3-year, before switch period; 3-year, after switch period	Primary: Annualized relapse rate over the 3-year post-switch treatment period Secondary: The proportion of patients relapse-free during the 3-year post-switch treatment period, mean change in EDSS score over 6 years	Primary: The annualized relapse rate was reduced by 77% (from 0.63 to 0.14) among patients who switched from IFNb to GA therapy (*P* value not reported). The annualized relapse rate was reduced by 71% (from 0.53 to 0.15) among patients who switched from IFNb to mitoxantrone therapy (*P* value not reported). The annualized relapse rate was reduced by 67% (from 0.52 to 0.17) among patients who switched from IFNb to GA therapy (*P* value not reported). The smallest reduction (57%, from 0.37 to 0.16) in the annualized relapse rate was observed in patients switched between different IFNb preparations (*P* value not reported). The annualized relapse rate was reduced by 75% (from 0.8 to 0.2) in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs IFNb-1a (Rebif®) 22 µg SC three times weekly for 3 years, subsequently switched to GA, IFNb-1a 44 µg SC, IFNb-1b, or mitoxantrone* therapy for additional 3 years vs IFNb-1a (Rebif®) 44 µg SC three times weekly for 3 years, subsequently switched to IFNb-1b, GA or mitoxantrone* therapy for additional 3 years vs IFNb-1a (Avonex®) 30 µg IM once weekly for 3 years, subsequently switched to IFNb-1b, IFNb-1a 44 µg SC, GA or mitoxantrone* therapy for additional 3 years vs IFNb or GA therapy for 6 years (reference cohort)				reference group over 6 years of therapy (*P* value not reported). Secondary: The proportion of relapse-free patients increased from 55% to 68% after switching to a different IFNb preparation (*P* value not reported). The proportion of relapse-free patients increased from 16% to 68% after switching from IFNb to GA therapy due to inadequate efficacy (*P* value not reported). The proportion of relapse-free patients increased from 71% to 80% after switching from IFNb to GA therapy due to adverse events (*P* value not reported). The proportion of relapse-free patients increased from 33% to 81% after switching from IFNb to mitoxantrone therapy (*P* value not reported). The proportion of relapse-free patients increased from 27% to 63% after switching from GA to IFNb therapy due to inadequate efficacy (*P* value not reported). The proportion of relapse-free patients decreased from 75% to 50% after switching from GA to IFNb therapy due to adverse events (*P* value not reported). There was no evidence of disability progression as evidenced by a lack of statistically significant change in EDSS scores among patients switching from IFNb to GA due to inadequate efficacy or those switching from IFNb to mitoxantrone ($P>0.05$). However, patients switching from one IFNb to another or GA to IFNb demonstrated a statistically significant disability progression ($P<0.05$). The change in EDSS scores was significantly higher among patients switching from GA to IFNb compared to those switching from IFNb to GA therapy ($P=0.0035$), suggesting a higher rate of disability progression in the latter group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant change from baseline in EDSS scores in the reference group 6 months after therapy initiation (*P* value not reported).
Clerico et al[48] IFNb-1b (Betaseron®) 0.25 mg SC every other day, IFNb-1a (Rebif®) 22 µg SC weekly, or IFNb-1a (Avonex®) 30 µg IM once weekly vs placebo	MA Double-blind, placebo-controlled, randomized trials of patients with CIS treated with either IFNb or GA therapy	N=1,160 (3 studies) 2-3 years	Primary: The proportion of patients who converted to CDMS Secondary: Side effects/adverse events	Primary: The proportion of patients converting to CDMS was significantly lower in the IFNb group compared to the placebo-treated group both at one year (OR, 0.53; 95% CI, 0.40 to 0.71; *P*<0.0001) and two years of follow-up (OR, 0.52; 95% CI, 0.38 to 0.70; *P*<0.0001). Secondary: The following side effects occurred more frequently in patients receiving IFNb therapy compared to placebo-treated patients: flu-like syndrome and injection-site reactions (*P*<0.00001). There was no statistically significant difference in the incidence of serious adverse events between the two groups (*P* value not reported).
Freedman et al[49] GA 20 mg SC weekly vs IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFNb-1a (Rebif®) 22-44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly	MA Double-blind, placebo-controlled, randomized, multicenter trials with a sample size >30 patients, that included patients at least 18 years of age diagnosed with a clinically-definite RRMS	N=2,351 (6 studies) up to 2 years	Primary: The proportion of patients relapse-free at 1 year, proportion of patients relapse-free at 2 years, proportion of patients progression-free at 2 years, proportion of patients free of gadolinium-enhancing lesions at 1 year Secondary: Not reported	Primary: Compared to placebo, a significantly greater proportion of patients receiving IFNb-1a 22-44 µg SC (AAR, 0.23; 95% CI, 0.14 to 0.33; *P* value not reported) and natalizumab were relapse-free at 1 year (AAR, 0.23; 95% CI, 0.17 to 0.30; *P* value not reported). The proportion of patients receiving IFNb-1a 30 µg IM or GA relapse-free at one year of therapy was not statistically different from placebo (*P* value not reported). Compared to placebo, a significantly greater proportion of patients receiving IFNb-1a 22-44 µg SC (AAR, 0.17; 95% CI, 0.09 to 0.26; *P* value not reported), IFNb-1b (AAR, 0.14; 95% CI, 0.04 to 0.25; *P* value not reported), and natalizumab were relapse-free at 2 years (AAR, 0.26; 95% CI, 0.20 to 0.33; *P* value not reported). The proportion of patients receiving GA relapse-free at 2 years of therapy was not statistically different from placebo (*P* value not reported). Compared to placebo, a significantly greater proportion of patients were progression-free at 2 years among patients receiving IFNb-1a 22-44 µg SC (AAR, 0.11; 95% CI, 0.01 to 0.2; *P* value not reported), IFNb-1a 30

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs natalizumab* 300 mg IV infusion every 4 weeks vs placebo				µg IM (AAR, 0.13; 95% CI, 0.03 to 0.23; *P* value not reported) and natalizumab (AAR, 0.12; 95% CI, 0.06 to 0.18; *P* value not reported). The proportion of patients progression-free at 2 years among patients receiving IFNb-1b or GA was not statistically different from placebo (*P* value not reported). Compared to placebo, a significantly greater proportion of patients were free of gadolinium-enhancing lesions at 1 year among patients receiving IFNb-1a 22-44 µg SC (AAR, 0.31; 95% CI, 0.17 to 0.44; *P* value not reported), IFNb-1a 30 µg IM (AAR, 0.12; 95% CI, 0.01 to 0.24; *P* value not reported) and natalizumab (AAR, 0.28; 95% CI, 0.23 to 0.33; *P* value not reported). The proportion of patients free of gadolinium-enhancing lesions at 1 year among patients receiving GA was not statistically different from placebo (*P* value not reported). Secondary: Not reported
Castelli-Haley et al[50] GA SC vs IFNb-1a (Rebif®) SC	CE, RETRO Patients (mean age 43) diagnosed with MS, with a procedure code, or outpatient prescription for GA or IFNb-1a, and insurance coverage starting at least 6 months before and extending through 24 months after the index date; in addition, a CU cohort could not have used other disease-modifying therapy within the study period and were required to	N=845 (ITT); N=410 (CU) 24 months	Primary: Costs (direct medical costs, including inpatient, outpatient and prescription drug cost), relapse rate (defined as hospitalization with an MS diagnosis or a 7-day steroid therapy. Secondary: Not reported	Primary: Compared to IFNb-1a therapy, patients in ITT cohort receiving GA experienced a significantly lower 2-year relapse rate (10.89% vs 5.92%; *P*=0.0305). Compared to IFNb-1a therapy, patients in the CU cohort receiving GA experienced a significantly lower 2-year relapse rate (9.09% vs 1.94%; *P*=0.0049). Compared to IFNb-1a therapy, patients in the ITT cohort receiving GA had significantly lower 2-year estimated direct medical expenses ($49,030 vs $41,786; *P*=0.0002). Compared to IFNb-1a therapy, patients in the CU cohort receiving GA had significantly lower 2-year estimated direct medical expenses ($57,311 vs $45,213; *P*=0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	have received the study medication within 28 days of study end			
Bell et al[51] GA 20 mg SC daily vs IFNb-1b (Betaseron®) 0.25 mg SC every other day vs IFN-1a (Rebif®) 22-44 µg SC three times weekly vs IFNb-1a (Avonex®) 30 µg IM once weekly vs symptomatic management	CE Patients diagnosed with RRMS in the United States	N=3,151 Up to 10 years	Primary: Incremental cost per QALY gained, cost per year spent in EDSS 0-5.5, cost per relapse-free year, cost per life-year gained Secondary: Not reported	Primary: The incremental cost per QALY gained was $258,465, $337,968, $416,301, $310,691 for GA, IM IFNb-1a, SC IFNb-1a and SC IFNb-1b, respectively, compared with symptomatic management. The incremental cost per year spent in EDSS 0-5.5 was $21,667, $28,293, $41,008, $27,860 for GA, IM IFNb-1a, SC IFNb-1a and SC IFNb-1b, respectively, compared with symptomatic management. The incremental cost per relapse-free year was $17,599, $24,327, $32,207, $23,065 for GA, IM IFNb-1a, SC IFNb-1a and SC IFNb-1b, respectively, compared with symptomatic management. The incremental cost per life-year gained was $2,076,622, $2,588,087, $3,378,626, $2,452,616 for GA, IM IFNb-1a, SC IFNb-1a and SC IFNb-1b, respectively, compared with symptomatic management. Consequently, compared to symptomatic management alone, GA was found to be the most cost-effective immunomodulatory therapy option for MS. Secondary: Not reported
Prosser et al[52] GA vs IFNb-1b (Betaseron®)	CE Hypothetical cohorts of patients with non-primary progressive MS	N=not reported 10 years	Primary: Net gain in quality-adjusted life expectancy, incremental cost-effectiveness ratios in dollars per QALY gained	Primary: 10-year therapy with IFNb-1a was associated with the largest gain in quality-adjusted life expectancy (QALY=7.955) with an incremental cost-effectiveness ratio of $2,200,000/QALY for women and $1,800,000/QALY for men, compared with no treatment. For 5-year treatment duration, no treatment strategy was associated with more quality-adjusted life years compared to alternative treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs IFNb-1a (Avonex®) vs no treatment Details of the clinical studies, including medication doses, used for the CE were not reported.			Secondary: Not reported	Cost-effectiveness ratios were similar across all treatment groups. Secondary: Not reported

*Not included in this review.
Drug regimen abbreviations: IFNb=interferon beta, IM=intramuscularly, IV=intravenous, GA=glatiramer acetate, SC=subcutaneously, TIW=three times weekly
Study abbreviations: AAR=absolute risk reduction, AB=assessor-blind, AMTD=adjusted mean treatment difference, CE=cost-effectiveness study, CI=confidence interval, CU=continuous use, DB=double blind, ES=extension study, HR=hazard ratio, I=international, ITT=intention-to-treat, MA=meta analysis, MC=multi-center, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PH=post-hoc analysis, PM=post-marketing, PRO=prospective, RETRO=retrospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SE=standard error
Miscellaneous abbreviations: BOD=burden of disease, BPF=brain parenchymal fraction, CDMS=clinically definite multiple sclerosis, CIS=clinically isolated syndrome, CUA=combined unique active, EDSS=expanded disability status scale, GA=glatiramer acetate, KFS=Kurtzke functional score, MRI=magnetic resonance imaging, MS=multiple Sclerosis Nab=neutralizing antibody, QALY=quality-adjusted life years, RRMS=relapsing-remitting MS, SPMS=secondary progressive MS, VAS=visual analogue scale, WBC=white blood cell

Special Populations

Short-term cohort studies have recently been performed in children and adolescents with multiple sclerosis (MS). The side effects of treatment with glatiramer acetate and the beta interferons appear to be similar to those observed with adults; however, the long-term efficacy and safety are unknown. As a result of the potential for physical and cognitive disabilities associated with MS, it is reasonable to offer these treatments to children and adolescents.[56] While glatiramer acetate is pregnancy category B and beta interferons are pregnancy category C, all MS biologic response modifiers are discontinued during pregnancy and relapses are treated with steroids.[6,8]

Table 5. Special Populations[1-4]

Generic Name (Trade name)	Population				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Glatiramer acetate (Copaxone®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Not reported	B	Not known; importance of drug administration to mother should be determined.
Interferon beta-1b (Betaseron®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Not reported	C	Not known; importance of drug administration to mother should be determined.
Interferon beta-1a (Rebif®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Hepatic dose adjustment may be necessary.	C	Not known; importance of drug administration to mother should be determined.
Interferon beta-1a (Avonex®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Hepatic dysfunction is a precaution.	C	Not known; importance of drug administration to mother should be determined.

Adverse Drug Events

Adverse events of beta interferons (Table 6) include influenza-like symptoms, injection site reactions, pain in the joints and muscles, fatigue and headache.[1-3] In clinical trials, adverse effects related to beta interferon therapy were dose related and transient.[11,26,31] High dose/high frequency interferons have been associated with more side effects than low dose/once weekly interferons. Most adverse effects develop within the first 6 months of therapy and resolve with continued use. In March 2005, the Food and Drug Administration recommended the labeling of Avonex® to include a warning of potential serious hepatotoxicity that may lead to rare cases of severe hepatic injury and/or hepatic failure. Rebif® also has a similar warning of potential hepatic injury.[2]

In pre-marketing studies, 10% of patients treated with glatiramer acetate experienced a transient, self-limited, systemic reaction of flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria immediately following injection.[4]

Table 6. Adverse Drug Events [1-4]

Adverse Event	Glatiramer acetate (%)	P* (%)	Interferon beta-1b† (%)	P* (%)	Interferon beta-1a‡ (%)	P* (%)	Interferon beta-1a§ (%)	P* (%)
Abdominal pain	-	-	16	11	20-22	17	8	6
Arthralgia or myalgia	24	19	23	14	25	20	29	22
Asthenia	41	38	53	48	-	-	24	18
Chest pain	21	11	-	-	6-8	5	5	2
Headache	-	-	50	43	65-70	63	58	55
Hypertonia	22	18	40	33	6-7	5	-	-
Influenza-like symptoms	19	17	57	37	56-59	51	49	29
Injection site reaction	40-73	6-38	78	26	89-92	39	6-8	2-6
Leukopenia	-	-	13	4	28-36	14	-	-
Nausea	22	17	-	-	-	-	23	19
Pain	28	25	42	35	-	-	23	21
Vasodilatation	27	10	-	-	-	-	2	0

*Placebo.
† Betaseron®.
‡ Rebif®.
§ Avonex®.

Contraindications / Precautions

Table 7. Contraindications / Precautions[1-4]

Severity	Concern	Affected Agents
Contraindications	Hypersensitivity to product	Beta interferons and glatiramer acetate
	Hypersensitivity to albumin	Interferon beta-1b, Interferon beta-1a (Rebif®) and Interferon beta-1a (Avonex®)
	Hypersensitivity to mannitol	Glatiramer acetate
Warnings	Depression and Suicide	Beta interferons
	Anaphylaxis	Beta interferons
	Decreased Peripheral Blood Counts	Interferon beta-1a (Avonex®)
	Hepatic Injury	Interferon beta-1a
	Injection Site Necrosis	Interferon beta-1b
Precautions	Seizure	Interferon beta-1a
	Cardiomyopathy and Congestive Heart Failure	Interferon beta-1a (Avonex®)
	Autoimmune Disorders	Interferon beta-1a (Avonex®)

Drug Interactions

Due to its potential to cause neutropenia, lymphopenia and hepatic injury, patients must be monitored when interferon beta-1a (Rebif®) is given in combination with another agent that can cause myelosuppression or hepatic injury.[2]

Table 8. Drug Interactions[1-4]

Generic Name	Interacting Medication or Disease	Potential Result
Biological response modifiers (beta interferons)	Live vaccines	Beta interferons can decrease the immune response, resulting in an increased risk of infection by live vaccines.

Dosage and Administration

Table 9. Dosing and Administration[1-4]

Generic Name (Trade name)	Adult Dose	Pediatric Dose	Availability
Glatiramer (Copaxone®)	20 mg subcutaneously daily	Safety and efficacy in children <18 years of age have not been established.	Prefilled syringe: 20 mg
Interferon beta-1b (Betaseron®)	Initial, 0.0625 mg subcutaneously every other day; maintenance, 0.25 mg subcutaneously every other day	Safety and efficacy in children <18 years of age have not been established.	Single use vial: 0.3 mg lyophilized powder
Interferon beta-1a (Rebif®)	Initial, 20% of maintenance dose; maintenance, 22-44 µg subcutaneously three times a week	Safety and efficacy in children <18 years of age have not been established.	Prefilled syringe: 8 µg 22 µg 44 µg
Interferon beta-1a (Avonex®)	30 µg intramuscularly once a week	Safety and efficacy in children <18 years of age have not been established.	Single use lyophilized powder vial and prefilled syringe: 30 µg

Clinical Guidelines

Table 10. Clinical Guidelines [10,13,57-59]

Clinical Guideline	Recommendations
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) and the Multiple Sclerosis Council for Clinical Practice Guidelines: **Disease Modifying Therapies in Multiple Sclerosis (2002)**[10]	Interferon Beta (IFNb) • It is appropriate to consider IFNb for treatment in any patient who is at high risk for developing clinically definite Multiple Sclerosis (MS), or who already has either relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) with relapses. • The effectiveness of IFNb in patients with SPMS but without relapses is uncertain. • There is insufficient evidence to determine if certain MS patients (e.g., those with more attacks or at earlier disease stages) may be better candidates for therapy. • It is probable that there is a dose-response curve associated with the use of IFNb; however, it is possible that a portion of this apparent effect may instead be due to differences in the frequency of IFNb administration. • It is probable that the route of administration of IFNb is not clinically important; however, the side effect profile does differ between routes of administration. • There is no known clinical difference amongst the different types of IFNb; although, this has not been thoroughly studied. • Treatment with IFNb is associated with the production of neutralizing antibody (Nab). The rate of NAb production appears to be reduced with IFNb-1a treatment compared with IFNb-1b treatment. The biologic effect of NAb is uncertain, but the presence of Nab may be associated with a reduction in clinical effectiveness of IFNb treatment.

Clinical Guideline	Recommendations
	Glatiramer Acetate (GA) • It is appropriate to consider GA for treatment in any patient who has RRMS. • GA may also be helpful in patients with progressive disease, but there is no convincing evidence.
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: **Neutralizing Antibodies to Interferon Beta: Assessment of Their Clinical and Radiographic Impact: an Evidence Report (2007)**[13]	• It is probable that the presence of NAb, especially in persistently high titers, is associated with a reduction in the radiographic and clinical effectiveness of IFNb treatment. • It is probable that the rate of NAb production is less with IFNb-1a treatment compared to IFNb-1b treatment. However, the magnitude and persistence of any difference in between these forms of IFNb is difficult to determine. • It is probable that the prevalence of NAbs to IFNb is affected by ≥1 of the following: formulation, route of administration, dose and/or frequency of administration.
National Clinical Advisory Board of the National Multiple Sclerosis Society. **MS Disease Management Consensus Statement (2007)**[57]	• Initiation of treatment with an IFNb or GA should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease. • Initiation of treatment with an IFNb or GA may also be considered for selected patients with a first attack who are at high risk of MS. • Access to medication should not be limited by the frequency of relapses, age or level of disability. • Treatment should not to be discontinued while insurers evaluate for continuing coverage of treatment. • Therapy should be continued indefinitely, except for the following circumstances: clear lack of benefit, intolerable side effects or availability of better therapy. • The most appropriate agent should be selected on an individual basis. • Transition from one disease-modifying agent to another should occur only for medically appropriate reasons. • IFNb or GA is not recommended for use by women who are trying to become pregnant, are pregnant or are nursing mothers.
National Institute for Clinical Excellence (NICE): **Beta Interferon and Glatiramer Acetate for the Treatment of Multiple Sclerosis (2002)**[58]	• In the health technology assessment, the long-term benefits of IFNb or GA therapy in the treatment of MS have been questioned following a review of clinical and cost effectiveness; however, the risk sharing scheme is provided.
National Institute for Clinical Excellence (NICE): **Management of Multiple Sclerosis in Primary and Secondary Care (2004)**[59]	RRMS IFNb Therapy Patient Conditions • Able to walk ≥100 meters without assistance • ≥2 clinically significant relapses in the past 2 years • ≥18 years • No contraindications to therapy RRMS GA Therapy Conditions • Able to walk ≥100 meters without assistance • ≥2 clinically significant relapses in the past 2 years • ≥18 years • No contraindications to therapy

Clinical Guideline	Recommendations
	SPMS IFNb Therapy Conditions • Able to walk ≥100 meters without assistance • ≥2 disabling relapses in the past 2 years • Minimal increase in disability due to gradual disease progression during the past 2 years • ≥18 years • No contraindications to therapy MS Patients Considering Treatment with IFNb Should Agree on the Following Discontinuation Criteria Prior to Initiating Therapy • Intolerable side effects • Pregnancy • ≥2 disabling relapses within 12 months • Secondary progression with an increase in disability over a 6-month period • Loss of ability to walk for >6 months MS Patients Considering Treatment with GA Should Agree on the Following Discontinuation Criteria Prior to Initiating Therapy • Intolerable side effects • Pregnancy • ≥2 disabling relapses within 12 months • Development of SPMS • Loss of ability to walk for >6 months

Conclusions

Interferon beta (IFNb)-1b, interferon beta-1a administered subcutaneously (SC), interferon beta-1a administered intramuscularly and glatiramer acetate (GA) are Food and Drug Administration (FDA) approved for the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS).[1-4] In addition, IFNb-1b and the IFNb-1a formulations administered intramuscularly are FDA approved for the treatment of patients with first clinical episode and magnetic resonance imaging (MRI) evidence of Multiple Sclerosis (MS).[1-3]

IFNbs and GA therapies have been shown to decrease MRI lesion activity, prevent relapses, delay disease progression and ultimately reduce disability from MS.[20-52] In general, patients can expect a 30% reduction in relapse rates during a two-year period following treatment initiation with IFNb or GA.[11] Head-to-head clinical trials have found IFNb and GA therapy to be comparable in terms of efficacy.[20-52] Several studies demonstrated an improved tolerability at the cost of a decreased therapeutic response with the low dose IFNb-1a IM formulation compared with the higher dose subcutaneous IFNb-1a product.[40-41]

The American Academy of Neurology and the National Multiple Sclerosis Society recommend the utilization of biologic response modifiers in MS patients.[10] The best evidence for effectiveness has been in patients with RRMS, but therapy may also be considered in certain patients with clinically isolated syndrome (CIS) and progressive forms of the disease.[6,8,10-11] The National Institute for Clinical Excellence has adopted a risk sharing scheme that identifies appropriate candidates for therapy based upon pre-determined measures.[59] The organization also recommends specific criteria for discontinuing therapy. Pediatric MS is rare and understudied. In general, treatment recommendations for adults are adapted to children with MS.[56] Additional studies are needed to establish the role of biologic response modifiers in patients with progressive MS and in children with MS.

While great strides have been made in the search for a safe and effective treatment for patients suffering from MS, many patients fail the initial biologic response modifier therapy primarily due to intolerable adverse effects or perceived inadequate efficacy.[14-15] Clinical trials have shown that patients switching from IFNb to GA therapy and vice versa, due to poor response, achieve a significant reduction in relapse

rates and a delay in disease and disability progression.[14,16-17] The guidelines suggest that all first line MS biologic response modifiers should be made accessible and the choice of initial treatment should be based on patient-specific factors.[10,57] Premature discontinuation rate is high among patients with MS; therefore factors that will maximize adherence should be considered when initiating therapy. Failure with one first-line agent does not necessitate failure to another. Therefore, patients experiencing an inadequate response or drug-induced adverse events should be switched to a different biologic response modifier.[14-15]

Recommendations

In recognition of the established safety and efficacy of these agents for the treatment of Multiple Sclerosis (MS), as well as their Food and Drug Administration (FDA) labeled indications, no changes are recommended to the current approval criteria.

Avonex®, Rebif®, Betaseron® and Copaxone® are preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

Tysabri® requires prior authorization with the following approval criteria:

- The patient has a diagnosis of relapsing multiple sclerosis and has already been stabilized on Tysabri®.

OR

- Diagnosis is relapsing multiple sclerosis and the patient has a documented side effect, allergy, treatment failure, or contraindication to at least two preferred drugs.

References

1. Avonex ® [package insert]. Cambridge, MA: Biogen IDEC, Inc, 2006 Nov.
2. Rebif® [package insert]. New York, NY: Pfizer, 2008 Apr.
3. Betaseron® [package insert]. Montville, NJ: Bayer Healthcare Pharmaceuticals, 2007 Oct.
4. Copaxone® [package insert]. Kansas City, MO: Teva, 2007 Nov.
5. Thrower B. Clinically isolated syndromes: predicting and delaying multiple sclerosis. Neurology. 2007; 68(supp4):S12-5.
6. Miscellaneous Therapeutic agents 28:00, Biological response modifiers. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2008 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2008 [cited 2008 Nov 22]. Available from: http://online.statref.com.
7. Kappos L. Interferons in multiple sclerosis. Neurol Clin. 2005;23:189-214.
8. Olek MJ. Treatment of relapsing-remitting multiple sclerosis in adults. In: Rose, BD, ed. UpToDate. Waltham, Mass: UpToDate, 2008.
9. Olek MJ. Treatment of progressive multiple sclerosis in adults. In: Rose, BD, ed. UpToDate. Waltham, Mass: UpToDate, 2008.
10. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology.2002; 58(2):169-78.
11. Galetta SL, Markowitz C, Lee AG. Immunomodulatory agents for the treatment of relapsing multiple sclerosis. Arch Intern Med. 2002; 162:2161-9.
12. Sorensen PS, Deisenhammer F, Duda P, et al. for the EFNS Task Force on Anti-IFN-beta Antibodies in Multiple Sclerosis. Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. Eur J Neurol. 2005;12(11):817-27.
13. Goodin DS, Frohman EM, Hurwitz B, et al. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2007;68(13):977-84.
14. Coyle PK. Switching algorithms: from one immunomodulatory agent to another. J Neurol. 2008; 255(Suppl 1):44-50.
15. Portaccio E, Zipoli V, Siracusa G, Sorbi S, Amato MP. Long-term adherence to interferon β therapy in relapsing-remitting multiple sclerosis. Eur Neurol. 2008; 59:131-5.
16. Caon C, Din M, Ching W, Tselis A, Lisak R, Khan O. Clinical course after change of immunomodulating therapy in relapsing-remitting multiple sclerosis. European Journal of Neurology. 2006; 13:471-4.
17. Zwibel HL. Glatiramer acetate in treatment-naïve and prior interferonb-1b-treated multiple sclerosis patients. Acta Neurol Scand. 2006; 113:378-86.
18. Tysabri® [package insert]. Cambridge, MA: Biogen Idec Inc., 2008 Oct.
19. Novantrone® [package insert]. Rockland, MA: Serono, Inc., 2007 Apr.
20. Boneschi FM, Rovaris M, Johnson KP, et al. Effects of glatiramer acetate on relapse rate and accumulated disability in multiple sclerosis: meta-analysis of three double-blind, randomized, placebo-controlled clinical trials. Multiple Sclerosis. 2003; 9:349-55.
21. Miller A, Spada V, Beerkircher D, Kreitman RR. Long-term (up to 22 years), open-label, compassionate-use study of glatiramer acetate in relapsing-remitting multiple sclerosis. Multiple Sclerosis. 2008; 14:494-9.
22. Carmona O, Casado V, Moral E, et al. Interferon-β1b in multiple sclerosis: effect on progression of disability and clinical markers of treatment response. Eur Neurol. 2008; 60:279-84.
23. PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. Lancet. 1998; 352:1498-504.
24. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. Neurology. 2006; 67:944-53.
25. Coppola G, Lanzillo R, Florio C, et al. Long-term clinical experience with weekly interferon beta-1a in relapsing multiple sclerosis. Eur J Neurol. 2006; 13:1014-21.

26. Flechter S, Vardi J, Rabey JM. Comparison of glatiramer acetate (Copaxone®) and interferon β-1b (Betaseron®) in multiple sclerosis patients: an open-label 2-year follow-up. J Neurol Sci. 2002; 197:51-5.
27. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, Stubinski B, Uitdehaag BMJ. Comparison of subcutaneous acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer acetate in Relapsing MS Disease [REGARD] study): a multicenter, randomized, parallel, open-label trial. Lancet Neurol. Oct .2008; 7:903-14.
28. Koch-Henriksen N, Sorensen PS, Christensen T, et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurol. 2006;66:1056-60.
29. Baum K, O'Leary C, Coret Ferrer F, Klímová E, Procházková L, Bugge J. Comparison of injection site pain and injection site reactions in relapsing-remitting multiple sclerosis patients treated with interferon beta-1a or 1b. Mult Scler. 2007 Nov;13(9):1153-60.
30. Barbero P, Bergui M, Versino E, et al. Every-other-day interferon beta-1b versus once weekly interferon beta-1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. Multiple Sclerosis. 2006;12:72-6.
31. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomized multicentre study (INCOMIN). Lancet. 2002;359:1453-60.
32. Minagara A, Murray TJ. Efficacy and tolerability of intramuscular interferon beta-1a compared with subcutaneous interferon beta-1a in relapsing MS: results from PROOF. Curr Med Res Opin. 2008; 24(4):1049-55.
33. Murray TJ. Rationale and design of the prospective and retrospective study of avonex and rebif (PROOF) for the treatment of relapsing-remitting multiple sclerosis. Curr Med Res Opin. 2004; 20(1):25-30.
34. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE trial. Neurol. 2002;59:1496-506.
35. Panitch H, Goodin D, Francis G, et al. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. J Neurol Sci. 2005;239:67-74.
36. Schwid SR, Thorpe J, Sharief M, et al. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis. The EVIDENCE study. Arch Neurol. 2005;62:785-92.
37. Schwid SR, Panitch HS. Full results of the evidence of interferon dose-response European North American comparative efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high dose, high-frequency interferon β-1a for relapsing multiple sclerosis. Clin Ther. 2007; 29(9):2031-48.
38. Traboulsee A, Sabbagh A AL, Bennett R, Chang P, Li DKB. Reduction in magnetic resonance imaging T2 burden of disease in patients with relapsing-remitting sclerosis: analysis of 48-week data from the EVIDNCE (evidence of interferon dose-response: European North American comparative efficacy) study. BMC Neurol. 2008 Apr 21;8:11.
39. Khan OA, Tselis AC, Kamholz JA, et al. A prospective, open-label treatment trial to compare the effect of IFN β-1b (Betaseron®), and glatiramer acetate (Copaxone®) on the relapse rate in relapsing-remitting multiple sclerosis. Eur J Neurol. 2001;8:141-8.
40. Khan OA, Tselis AC, Kamholz JA, Garbern JY, Lewis RA, Lisak RP. A prospective, open-label treatment trial to compare the effects of IFNb-1a (Avonex®), IFNb-1b (Betaseron®), and glatiramer acetate (Copaxone®) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. Multiple Sclerosis. 2001; 7:349-53.
41. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaseron, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand. 2006; 113:283-7.
42. Rio J, Tintore M, Nos C, et al. Interferon beta in relapsing-remitting multiple sclerosis: an eight years experience in a specialist multiple sclerosis centre. J Neurol. 2005; 252:795-800.
43. Trojano M, Liguori M, Paolicelli D, et al. Interferon beta in relapsing-remitting multiple sclerosis: an independent postmarketing study in southern Italy. Multiple Sclerosis. 2003;9:451-7.
44. Trojano M, Pellegrini F, Fuiani A, et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. Ann Neurol. 2007; 61:300-6.

45. Limmroth V, Malessa R, Zettl UK, et al. Quality assessments in multiple sclerosis therapy (QUASIMS). J Neurol. 2007; 254:67-77.
46. Haas J, Firzlaff M. Twenty-four-month comparison of immunomodulatory treatments – a retrospective open label study in 308 RRMS patients treated with beta interferons or glatiramer acetate (Copaxone). Eur J Neurol. 2005; 12:425-31.
47. Carra A, Onaha P, Luetic G, et al. Therapeutic outcome 3 years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. European Journal of Neurology. 2008; 15:386-93.
48. Clerico M, Faggiano F, Palace J, Rice G, Tintorè M, Durelli L. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. Cochrane Database Syst Rev. 2008 Apr 16; (2):CD005278.
49. Freedman MS, Hughes B, Mikol DD, Bennett R, Cuffel B, Divan V, LaVallee N, Al-Sabbagh A. Efficacy of disease-modifying therapies in relapsing remitting multiple sclerosis: a systematic comparison. Eur Neurol. 2008; 60(1):1-11.
50. Castelli-Haley J, Oleen-Burkey MKA, Lage MJ, Johnson KP. Glatiramer acetate versus interferon beta-1a for subcutaneous administration: comparison of outcomes among multiple sclerosis patients. Adv Ther. 2008;25(7):658-73.
51. Bell C, Graham J, Earnshaw S, Oleen-Burkey M, Castelli-Haley J, Johnson K. Cost-effectiveness of four immunomodulatory therapies for relapsing-remitting multiple sclerosis: a Markov model based on long-term clinical data. J Manag Care Pharm. 2007 Apr;13(3):245-61.
52. Prosser LA, Kuntz KM, Bar-OR A, Weinstein MC. Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. Value Health. 2004 Sep-Oct;7(5):554-68.
53. Alsop JC for the PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group. Interferon β-1a in MS: results following development of neutralizing antibodies in PRISMS. Neurology. 2005; 65:48-55.
54. Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol. 2007; 61:14-24.
55. Rizvi SA, Agius MA. Current approved options for treating patients with multiple sclerosis. Neurology. 2004 Dec 28;63(12 Suppl 6):S8-14.
56. Lotze TE. Treatment and prognosis of pediatric multiple sclerosis. In: Rose, BD, ed. UpToDate. Waltham, Mass: UpToDate, 2008.
57. National Clinical Advisory Board of the National Multiple Sclerosis Society. MS Disease Management Consensus Statement. 2007 [cited 2008 Nov 20]. Available from www.nationalmssociety.org.
58. National Institute for Clinical Excellence (NICE): Beta Interferon and glatiramer acetate for the treatment of multiple sclerosis. 2002 [cited 2008 Nov 20]. Available from http://www.nice.org.uk.
59. National Institute for Clinical Excellence (NICE). Multiple sclerosis: national clinical guideline for diagnosis and management in primary and secondary care. 2004 (cited 2008 Nov 20). Available from http://www.rcplondon.ac.uk/pubs/books/ms/.